Please add new claim 21 as set out below:

21. A method as claimed in claim 1 wherein the specific binding assay of step ii) is a fluorescence polarization immunoassay.

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REMARKS

I. Preliminary Comments

Applicant, through the undersigned attorney wish to thank the Examiner and her supervisor for the courtesy extended during the telephonic interview conducted on September 5, 2001. The unexpected results obtained by practice of the claimed invention were discussed at the interview as was the possibility of submission of a Declaration addressing those unexpected results.

The subject matter of claim 21 submitted herewith is described at page 18, line 29 through page 19, line 19 and does not enter new matter into the application.

II. Outstanding Rejections

Claims 1, 2 and 4-14 stand rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to distinctly claim the subject matter of the invention.

Claims 1, 2, 4, 5, 8-11, and 13-20 stand rejected under 35 U.S.C. §103(a) as being obvious over Cook (Research Focus 1(7): 287-94, 1996) (hereinafter "Cook (1)") in view of Lundin *et al.* (U.S. 5,558,986) (hereinafter "Lundin").

Claims 6-7 and 12 stand rejected under U.S.C. §103(a) as being unpatentable over Cook (1) in view of Lundin, and in further view of Cook (WO 94/26413) (hereinafter "Cook (2)").

III. Patentability Arguments

A. The Rejections Under 35 U.S.C. §112, Second Paragraph Should be Withdrawn

The rejection of claims 1-14 under 35 U.S.C. §112, second paragraph, should be withdrawn for the following reasons. Claim 1 has been amended in the manner suggested by the Examiner to more clearly recite that the assay is a specific binding assay. Claims 17 and 18 have been amended to more clearly recite the labeling of the specific binding partner. No new matter is entered thereby and the rejection under 35 U.S.C. §112, second paragraph may now be withdrawn.

B. The Rejections Under 35 U.S.C. §103(a) Should be Withdrawn

The rejection of claims 1, 2, 4, 5, 8-11 and 13-20 over Cook (1) in view of Lundin under 35 U.S.C. §103(a) should be withdrawn because one of ordinary skill in the art and lacking the hindsight knowledge of Applicant's invention would not have expected the use of a cyclodextrin sequestering agent in the enzyme-mediated amplification assays of Lundin to be of particular benefit in a specific binding-type assay of the invention.

Submitted herewith is a copy of the Rule 132 Declaration which will be signed by Jeffrey Kenneth Horton, the inventor of the claimed subject matter directed to the following points. The signed Declaration has not yet been returned to the undersigned attorney but will be provided to the Examiner as soon as it is received. The methods claimed in the above-identified patent application are directed to specific binding assays in which the presence of an analyte in a sample is assayed for by steps including reaction of a specific binding partner for the analyte with the analyte to form a specific binding partner-analyte complex and detection of that complex. (One example of a specific binding partner-analyte complex is the complex formed

between an antigen and an antibody specific for that antigen.) More particularly, the method of the invention includes the steps of mixing a sample of cells with a cell lysis agent to provide a lysed cellular sample, mixing the lysed cellular sample with a cyclodextrin sequestrant for the cell lysis reagent, and performing the specific binding assay in the presence of that sequestrant.

The use of a cyclodextrin sequestrant for a cell lysis reagent is not taught in either Cook (1) or Cook (2) for the art of specific binding assays.

The use of a cyclodextrin sequestrant for a cell lysis reagent is known in Lundin for conducting various enzyme-mediated reactions. These enzyme-mediated reactions include firefly luciferase assays, polymerase chain reaction (PCR) nucleic acid amplification, and restriction enzyme digestions. Lundin does not teach the use of a cyclodextrin sequestrant for conducting specific binding assays.

Assays involving enzyme-mediated reactions, such as those of Lundin, differ from specific binding assays for a specific binding partner in that an enzyme-mediated reaction amplifies the record of the presence of the involved enzyme through the catalysis of the enzymatic reaction to produce a product. Because an enzyme is not consumed in a catalytic reaction the reaction will continue and product will be produced until the reactants are exhausted. Thus, even a minor amount of active enzyme will produce detectable product given sufficient time to complete the reaction. Put another way, even if a large proportion of enzyme is inactivated, any remaining active enzyme will eventually produce detectable product.

In contrast to an enzyme-mediated reaction, a specific binding reaction "consumes" the analyte "reactant". The amount of specific binding partner-analyte complex "product" produced will be limited to the amount of biologically active analyte. If a proportion of the analyte is inactivated by means of a cell lysis agent or otherwise, the remaining portion of

active analyte will not take the place of the inactive analyte. Thus, if a sufficiently large proportion of the analyte is inactivated, the remaining small amounts of specific binding partner-analyte complex may be undetectable.

For these reasons, the utility of a cyclodextrin sequestrant to provide positive assay results in an enzyme-mediated assay would not lead one of ordinary skill in the art to conclude that similar improvements could be attained in a specific binding assay. Because a specific binding reaction does not include an amplification step in the manner that an enzyme-mediated reaction does, specific binding assays were recognized to be significantly more sensitive to inactivation such as caused by cell lysis reagents. Accordingly, it would not have been clear to one of ordinary skill in the art that incorporation of a cyclodextrin sequestrant would solve the inactivation problem caused by cell lysis reagents and the rejection of claims 1, 2, 4, 5, 8-11 and 13-20 should be withdrawn.

Moreover, the rejection of claims 6, 7 and 12 over the combination of Cook (1), Lundin and Cook (2) should also be withdrawn for the reasons set out with respect to claim 1 above. While Cook (2) discloses various elements of the dependent claims including use of a multiwell system, it does not make up for the deficiencies of Cook (1) and Lundin in teaching the subject matter of independent claim 1. Accordingly, the rejection of claims 6, 7 and 12 should also be withdrawn.

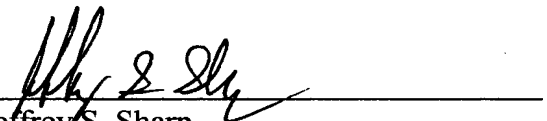
CONCLUSION

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned **"Version with markings to show changes made."**

In light of the foregoing amendments and remarks, it is believed that claims 1, 2 and 4-20 are in condition for allowance and a notice thereof is respectfully requested. Should the Examiner wish to discuss any further matter of form or substance, she is encouraged to contact undersigned attorney at the telephone number listed below.

Respectfully submitted,

MARSHALL, GERSTEIN & BORUN

By 

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October 22, 2001

VERSION WITH MARKINGS TO SHOW CHANGES MADE

Claims 1, 17 and 18 have been amended as set out below:

1. [Three Times Amended] A method of conducting a specific binding assay [assaying] for the presence of an analyte in a cell sample which method comprises the steps of:

i) mixing a sample of cells with a cell lysis reagent to provide a lysed cellular sample;

ii) mixing the lysed cellular sample with a specific binding partner of the analyte to perform a specific binding assay by forming a reaction mixture comprising a specific binding partner-analyte complex;

iii) mixing the lysed cellular sample with a cyclodextrin sequestrant for the cell lysis reagent, whereby the specific binding assay of step ii) is performed in the presence of the sequestrant; and

iv) detecting the presence of the specific binding partner-analyte complex the presence of which is indicative of the presence of the analyte in the sample.

17. [Amended] The method as claimed in claim 1, wherein the [assay reagents comprise] specific binding partner is labeled with a tracer.

18. [Amended] The method as claimed in claim 1, wherein the [assay reagents comprise a labeled assay reagent for detection wherein the] specific binding partner is labeled with a label [is] selected from the group consisting of radioactive isotope labels, enzyme-linked labels and fluorescent labels.

Please add new claim 21 as set out below:

21. A method as claimed in claim 1 wherein the specific binding assay of step ii) is a fluorescence polarization immunoassay.

APPENDIX OF PENDING CLAIMS (AFTER ENTRY OF AMENDMENT)

1. A method of conducting a specific binding assay for the presence of an analyte in a cell sample which method comprises the steps of:

i) mixing a sample of cells with a cell lysis reagent to provide a lysed cellular sample;

ii) mixing the lysed cellular sample with a specific binding partner of the analyte to perform a specific binding assay by forming a reaction mixture comprising a specific binding partner-analyte complex;

iii) mixing the lysed cellular sample with a cyclodextrin sequestrant for the cell lysis reagent, whereby the specific binding assay of step ii) is performed in the presence of the sequestrant; and

iv) detecting the presence of the specific binding partner-analyte complex the presence of which is indicative of the presence of the analyte in the sample.

2. The method as claimed in claim 1, wherein the cell lysis reagent is a detergent.

4. The method as claimed in claim 1 wherein the amount of cyclodextrin sequestrant is in the range of 1 - 5% of the said reaction mixture.

5. The method as claimed in claim 1, wherein steps i), ii) and iii) are all performed in a single reaction vessel.

6. The method as claimed in claim 1, wherein individual assays are performed in parallel in individual vessels which are wells of a multiwell plate.

7. The method as claimed in claim 5, wherein the cells are cultured in said vessel and are lysed in that vessel for assaying the analyte in that vessel.

8. The method as claimed in claim 1, wherein the assay of step ii) is a homogenous assay.

9. The method as claimed in claim 1, wherein the assay of step ii) is a scintillation proximity assay.

10. The method as claimed in claim 1, wherein the specific binding assay of step ii) is an immunoassay.

11. The method as claimed in claim 1, wherein the analyte is adenosine-3′, 5′-cyclic monophosphate, the cell lysis reagent is dodecyl trimethyl ammonium bromide and the sequestrant is α-cyclodextrin.

12. The method as claimed in claim 1, wherein the cells have been maintained in a culture medium, and step i) is performed in the presence of the culture medium.

13. The method as claimed in claim 1, wherein the intracellular or both intracellular and extracellular concentration of the analyte is measured and the analyte is selected from the group consisting of adenosine-3′,5′-cyclic monophosphate, interleukin-6 and prostaglandin E_2.

14. A kit, suitable for assaying for an analyte by the method as claimed in claim 17 which method further comprises the step of separating bound tracer from unbound tracer , comprising: a detergent; a sequestrant for the detergent; a specific binding partner of the analyte; a tracer; and separation means for separating bound tracer from unbound tracer.

15. The method as claimed in claim 1, wherein the specific binding assay is an immunoassay.

16. The method as claimed in claim 1, wherein the specific binding assay is a receptor binding assay.

17. The method as claimed in claim 1, wherein the specific binding partner is labeled with a tracer.

18. The method as claimed in claim 1, wherein the specific binding partner is labeled with a label selected from the group consisting of radioactive isotope labels, enzyme-linked labels and fluorescent labels.

19. A method as claimed in claim 1 further comprising the step of separating bound tracer from unbound tracer.

20. A kit suitable for assaying for an analyte by the method as claimed in claim 1, comprising a detergent, a cyclodextrin sequestrant for the detergent, and a specific binding partner for the analyte.

21. A method as claimed in claim 1 wherein the specific binding assay of step ii) is a fluorescence polarization immunoassay.